Loss of NARS1 impairs progenitor proliferation in cortical brain organoids and leads to microcephaly.

Journal: Nat Commun

Publication Year: 2020

Authors: Lu Wang, Zhen Li, David Sievert, Desiree E C Smith, Marisa I Mendes, Dillon Y Chen, Valentina Stanley, Shereen Ghosh, Yulu Wang, Majdi Kara, Ayca Dilruba Aslanger, Rasim O Rosti, Henry Houlden, Gajja S Salomons, Joseph G Gleeson

PubMed link: 32788587

Funding Grants: CIRM Graduate Student Training Grant for the Implementation of a Stem Cell Technology and Lab Management Program: Training in Stem Cell Sciences and Regenerative Medicine

Public Summary:
Asparaginyl-tRNA synthetase1 (NARS1) is a member of the ubiquitously expressed cytoplasmic Class IIa family of tRNA synthetases required for protein translation. Here, we identify biallelic missense and frameshift mutations in NARS1 in seven patients from three unrelated families with microcephaly and neurodevelopmental delay. Patient cells show reduced NARS1 protein, impaired NARS1 activity and impaired global protein synthesis. Cortical brain organoid modeling shows reduced proliferation of radial glial cells (RGCs), leading to smaller organoids characteristic of microcephaly. Single-cell analysis reveals altered constituents of both astrocytic and RGC lineages, suggesting a requirement for NARS1 in RGC proliferation. Our findings demonstrate that NARS1 is required to meet protein synthetic needs and to support RGC proliferation in human brain development.

Scientific Abstract:
Asparaginyl-tRNA synthetase1 (NARS1) is a member of the ubiquitously expressed cytoplasmic Class IIa family of tRNA synthetases required for protein translation. Here, we identify biallelic missense and frameshift mutations in NARS1 in seven patients from three unrelated families with microcephaly and neurodevelopmental delay. Patient cells show reduced NARS1 protein, impaired NARS1 activity and impaired global protein synthesis. Cortical brain organoid modeling shows reduced proliferation of radial glial cells (RGCs), leading to smaller organoids characteristic of microcephaly. Single-cell analysis reveals altered constituents of both astrocytic and RGC lineages, suggesting a requirement for NARS1 in RGC proliferation. Our findings demonstrate that NARS1 is required to meet protein synthetic needs and to support RGC proliferation in human brain development.